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- © COMPOUNDS OF S-TRIAZINE DERIVATIVES AND THEIR SALTS AND PROCESS FOR PRODUCTION OF SALD COMPOUNDS
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- (a) APPLICATION No. 143, 155 720526
- (60, 067/71) 710807 page 4 page 1 pag

No. OF CLAIMS 14 - No drawing

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as Collows:

1. A process for the preparation of a compound of the formula:

in which: R₁ is an alkyl group of 2 to 4 carbon atoms, cyclohexyl, phenyl or phonyl substituted by fluore, chiere, toda, mercapte, trifluoremethyl, ethoxy, nitro or methyl; R₂ is a hydrogen atom, methyl or othyl; and R₃ is pyridyl, an alkyl group of 1 to 5 carbon atoms, phenyl, p-danbutyl-bensyl, p-isobutyl-K-methylbensyl, p-tolyl, vinyl, hydroxyl or carbonyl, which process comprises teacting a substituted disymmediande of the general formula:

in which \mathbf{R}_1 and \mathbf{R}_2 have the same meaning as above, with a mirrile having the general formula:

r₇(H

in which and is pyridyl, an alkyl group of 1 to 5 carbon atoms, phenyl, p-isobutylbenzyl, p-isobutyl ——methyl benzyl, p-isolyl or vinyl, in the presence of a basic compound.

2. A process according to claim 1, wherein enid substituted dicyandiamide is: N-(n-busyl)dicyandiamide; N-isobutyldicyandiamide; N-cyclohexyldicyandiamide; N-cyclohexyldicyandiamide; N-cyclohexyldicyandiamide; N-(p-bromophenyl)dicyandiamide; N-(p-fluorophenyl)dicyandiamide; N-(p-methylbenzyl)dicyandiamide; N-(p-chlorophenyl)dicyandiamide; N-phenethyldicyandiamide; N-(N-pyridyl)-dicyandiamide; N-(5-isoquinolyl)dicyandiamide; N-ethyl-N-n-butyldicyandiamide; N-ethyl-N-phenyldicyandiamide; N-ethyl-N-ethyl-N-ethyl

dicyandlamide; W.N-diallydicyandiamide; W-(2,5-dichlorophrayl)dicyandiamide; N-nethyl-N-(n-trifluoromethylphenyl)dicyandiamide; or N-(2,5-diathaxyphenyl)dicyandiamide.

- 3. A process according to claim 1, in which said nitrile is:
 scetonitrile; propionitrile; n-butyronitrile; isobutyronitrile;
 scrylonitrile; allyloyanide; benzonitrile; p-methylbenzonitrile; p-chlorobenzonitrile; m-nitrobenzonitrile; Y-naphthyloyanide; benzyloyanide;
 p-isobutylbenzyloyanide; p-isobutyl-Y-methylbenzyloyanide; 3-cyanopyridine; or 4-cyanopyridine.
- 4. A process seconding to claim 2 in which said adtrile is:

 acetonitrile; promionitrile; u-butyronitrile; isobutyronitrile;

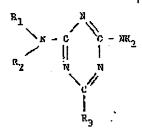
 acrylonitrile; allyicyanide; benzenitrile; p-wetbylbenzontrile; p-whlorobunzonttrile; m-uitrobenzonitrile; '\foraghthylcyanide; benzylayanide;

 p-isobutylbenzylcyanide; p-isobutyl- \foraghthylbenzylcyanide; 3-cyanopyridine; or 4-cyanopyridine.
- 5. A process according to claims 2, 3 or 4 to which said basic compound is selected from the group consisting of alkali carbonates, alkali hydroxides, metal alcoholates, alkali anddes, tertiary amines and quaternary ammonium salts.
- 6. A process securding to claims 2. 3 or 4 in which said carbonyl derivative is carbonic acid ester and in which said busic compound is a sodium alcoholate.
- 7. A process according to claims 2, 3 or 4 in which said carbonyl derivative is carbonic acid ester and in which said sodium placeholate is sodium methoxide.
- 8. A process according to claims 1 or 2 carried out in the presumes of one or more solvents selected from hydrocuchons, ethers, ketones, alcohols or other organic solvents, selected from methyl cellosolve, sthyl cellosolve, dioxanc or butanol.
- 9. A process according to claim: 3 or 4 carried out in the presence of one or more solvents selected from hydrocarbous, ethers, ketones, alcohols or other organic solvents, selected from methyl

cellosolve, ethyl cellosolve, diswane or butanol.

10. A process according to claim 1 including the step of forming pharmaceutically accoptable acid addition calts by reaction with un acid selected from the group comprising hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid, perchloric acid, formic acid, acetic acid, propionic acid, oxalic acid, succinic acid, glycolic acid, nicotinic acid, tartaric acid, maleic acid, nalic acid, lactic acid, pamoic acid, citric acid, ascorbic acid, methanesulphonic acid, salicyclic acid, benzoic acid or cyclohexaneoniphanic acid.

11. A compound selected from (a) those of the formula:



in which R₁ is an alkyl group of 2 to 4 carbon atoms, cyclobacyl, phenyl or phenyl substituted by fluore, chlore, iode, mercapte, trifluoromethyl, sthony or methyl, R₂ is a hydrogen atom, methyl or citiyl and R₃ is pyridyl, an alkyl group of 1 to 5 carbon atoms, phenyl, p-isobutylbenzyl, p-isobutyl-X-methylhenzyl, p-tolyl, vinyl, hydroxyl or carboxyl, whose over prepared by the process of claim 1 or by its choices chemical equivalents; and (b) phermaceutically acceptable acid addition calts of a compound of the formula 1, whenever prepared by the process of claim 10 or by its obvious chemical equivalents.

12. A compound of the formula

wherein R_I represents phenyl substituted by fluors, chinco, iodo,

mercapto, trifluorommethyl, phonyl, athoxy, mitro or mathyl and he represents pyridyl, an alkyl group of 1 to 3 carbon atoms, phenyl, p-isobutylbensyl or p-isobutyl-C-mathylbensyl whenever propared by the process of claim 1 or by its obvious chemical equivalents.

13. A pharmaceuticully acceptable and addition salt of a com-

$$R_1 - MH - C C - MH_2$$

wherein R₁ represents physical substituted by fluoro, chlore, indo, morcepto, trifluoromethyl, phenyl, othoxy, nitro or methyl and R₂ represents pyridyl, an alkyl group of I to 3 carbon atoms, phenyl, p-isobatylbenzyl, or p-isobatyl->(-methylbenzyl whenever prepared by the process of claim 1 or by its obvious chemical equivalents, and in which the acid is: hydrochloric acid, bydrobromic acid, subphuric acid, attic acid, phosphoxic acid, perchloric acid, formic acid, nextic acid, propionic acid, oxalic acid, succinic acid, glycolic acid, nicotinic acid, tartaric acid, maleic acid, nalic acid, lactic acid, pampic acid, extric acid, sacorbic acid, methanexulphuntle acid, salicyclic acid, benzoic acid or cyclobexanesulphumic acid, whenever prepared or produced by the process of claim 10 or by its obvious chemical equivalent.

1.4. As a compound of claim 12, 2-aminn-4-(N-ethylarilino)-6-(3-pyridy1)-1,3,5-triazine; 2-aminn-4-(N-ethylanilino)-6-ethyl-1,3,5-triazine; 2-aminn-4-(p-chlorosnilino)-6-phenyl-1,3,5-triazine; 2-aminn-4-(p-chlorosnilino)-6-methyl-1,3,5-triazine; 2-aminn-4-(n-butyl-aminn)-6-(3-pyridyl)-1,3,5-triazine; 2-aminn-4-eyelohexylaminn-6-(p-tolyl)-1,3,5-triazine; 2-aminn-4-(p-browountlino)-6-vivyl-1,3,5-triazine; 2-aminn-4-(p-browountlino)-6-vivyl-1,3,5-triazine; 2-aminn-4-(m-trifluorosnthylamilino)-6-(p-isobutylbenzyl)-1,3,5-triazine; 2-aminn-4-(y-trifluorosnthylamilino)-6-(p-isobutylbenzyl)-1,3,5-triazine; 2-aminn-4-(y-fluorosnthylamilino)-6-(p-isobutylbenzyl)-1,3,5-triazine;

nnilina)-6-ethyl-1,3,5-triazine; 2-amino-4-(y-batylamina)-6-(p-isobutyl-hanzyl)-1,3,5-triazine; 2-amino-4-(y-bromosullino)-6-athyl-1,3,5-triazine; and 2-amino-4-(p-mothylamilino)-6-mothyl-1,3,5-triazine; whenever prepared by the process of claims 2, 3 or 4 or by their obvious abumbeal equivalents.

This invention relates to a process for preparing novel s-triazlue derivatives and to the movel s-triazine derivatives so formed.

According to one aspect, therefore, the present invention provides novel s-triazine derivatives baving the following general formula:

10 In which: R₁ is an alkyl group of 2 to 4 carbon atoms, cyclohexyl, phenyl or phenyl substituted by fluoro, chiorn, lodo, mercapto, trifluoromethyl, ethoxy, nitro or mathyl; R₂ is a hydrogen atom, methyl or ethyl; and R₃ is pyridyl, an alkyl group of 1 to 5 carbon stoms, phenyl, p-isobutylhemsyl, p-fabbutyl-%-methylbensyl, p-tolyl, vinyl, hydroxyl or carboxyl, as well as pharmacoutically acceptable soid addition salts of these derivatives.

The invention also provides in snother of its aspects, a process for producing such s-trivaine decivatives which comprises reacting a substituted dicyenediaminde of the general formula:

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in which \mathbf{R}_1 and \mathbf{R}_2 have the same meaning as above, with a mitrile having the general formula

R, CN

in which a₃ is pyridyl, an alkyl group of 1 to 5 carbon atoms, phonyl, p-isobutylbenzyl, p-isobutyl-%-methylbenzyl, p-tolyl or vinyl, in the presence of a basic compound.

By mother aspect of this invention, pharmscentically acceptable acid addition salts of such movel s-triazines are provides by reaction of the s-triazine with an acid selected from the group coaprising hydrochloric acid, hydrobromic acid, sulphuric acid, plant acid.

phosphoric acid, percharge acid, formle acid, acetic acid, propionic acid, exalic acid, succinic acid, glycolic acid, oleotinic acid, tartaric acid, maleic acid, malic acid, lacete acid, pembic acid, exitric acid, escorbic acid, mothenesulphonic acid, enticyclic acid, benzoic acid or cyclobexenesulphonic acid.

If will be further understood that R₃ will sometimes change from one radical into another during the reaction for preparing the matterine derivatives or their salts; for example, R₃ may change from an alkoxycarbonyl radical into a carboxyl radical, and from a substituted alkyl radical into an hydroxyl radical.

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The compounds of a main aspect of the present invention may be used in pharmaceutical compositions and possess a wide range of bioactivity in, for example, birds and mammals including humans. Its bioactivity remarkably increases the secretion of induced corticoid in the hormone system.

Korcover, the starting materials used in the processes of other espects of the present invention, namely, the compounds of substituted disyandiaminde, and the ultrile are comporatively inexpensive and are available in large quantities; also, the yield of the process is excellent.

Bramplex of autiable substituted dicynuliamides which can be used in the process of one aspect of the present invention include:

N-(n-butyl)dicyandismide; R-ixabutyldicyandismide; M-vinyldicyandiamide; N-(n-pentenyl)dicyandiamide; N-cyclohexyldicyandiamide;

N-cyclohoptyldicyandiamide; N-(p-bromophenyl)dicyandiamide; K-(p-fluocophenyl)dicyandiamide; K-(p-mathylbenzyl)dicyandiamide; N-(p-chlorophenyl)dicyandiamide; K-phanethyldicyandiamide; N-(h-pyrldyl)dicyandiamide; N-(5-icoquinolyl)dicyandiamide; N-athyl-R-(n-butyl)dicyandiamide; N-ethyl-R-phenyldicyandiamide; N-othyl-R-(p-chlorophenyl)dicyandiamide; N,N-diallyldicyandiamide; N-(2,5-dichlorophenyl)dicyandiamide; N-aethyl-N-(m-trifluoromethylphenyl)dicyandiamide; and
N-(2,5-dichlorophenyl)dicyandiamide.

Examples of suitable officiles which can be used in the process of one aspect of the present invention include: acctonitile; propionitrile; n-butyronitrile; isobutyronitrile; acryimattrile; allylecysnide; henzonitrile; p-methylbenzonitrile; p-chlorobenzonitrile; m-mitrobenzonitrile; %-naphthyloysnide; benzyloysnide; p-isobutyl-benzyloysnide; p-tanbutyl-%-mothylbenzyloysnide; 3-cysnopyridine; and 4-cysnopyridine.

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In the process of one aspect of this invention, inorganic or organic compounds such as, for example, alkali carbonates, ulkali hydroxides, metal plepholstes, altali smides, tertiary mmines, quaternery ammonium salts or the like may be useful as the basic compounds. In the presence of which the reaction between the substituted dicyandiamide and the mitrile is conducted. It is possible that the reaction will take place in the absence of a solvent; however, generally the reactions may better be carried out in the presence of the solvent. Hydrocarbons, ethora, ketonea, alcohole and/or the other organic solvents way be used so the solvent, provided that the solvent does not interfere with the reaction; methyl cellosolve, othyl cellosolve, dioxene or butaunol are particularly preferred. In the case where an excess of the mitrile is used, the solvent need not be used in the reaction. The reaction may be effected at a temperature of 50 to 200°C., but preformbly near the temperature of this reflux. The reaction will normally take from 20 minutes to 24 hours to teach completion, at which time the s-triazine derivatives can be obtained in high yields.

The basic compound may be selected from the group consisting of alkali carbonates, alkali hydroxides, meral alcoholates, sitali smides, tertiary amines and quaternary amountum salts, and the carbonyl derivative may be carbonal acid ester in which the basis compound is a sodium alcoholate.

The s-triazine can be used in the form of a free b. a or as a sait produced by reacting the free base and an acid, for en upla, bydrochloric acid, bydrohromic acid, sulphurle acid, mitric acid,

phosphoric actd, perchloric acid, formic wold, acetic acid, propionic acid, oxalic acid, succinic acid, glycolic acid, nicotinic acid, furturale acid, maleic acid, malic acid, lactic acid, pambic acid, citric acid, succeptic acid, methanesulphonic acid, salleyclic acid, benzoic acid, or cyclohexanesulphamic acid or other pharmaceutically acceptable acids.

The utility of vortions aspects of this invention is shown hereinafter in the

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pharmomentical data.

In Table 1 below, R_1 , R_2 and R_3 of the triazines obtained in the following examples and of other triazines obtained by similar processes are shown. Table 1 also provides the melting points thereof and their code numbers, provided with ${}^tM^{rt}$ signs.

Table 1

	Product	R ₁ N -	R ₃ -	Melting point (°C)
10.	мо626	n-butylazino	p-1sobutylbenzyl	99.5-101
	H0632	n-butylandno	3-pyridyl	1445-1455
•	M1403 ·	o-methylauilino	githy l	196-198
	K1431	o-mothylanilino	4-py¢&dy:L	193-194
	M1602	p-mathylanilino	methy1	204~205
	M1613	p-methylanilino	phony1	156-158
	KT631	p-wethylanilino	4-pyridyl	200-201
	x1632-	p-methylamiline	O-pyridyl	200-201
	%1702	p-fluoroamilimo	nethyl	203-204
	к1 79 3	p-Pluorosullino	ethyl	160-161
20	30.704	p-fluoroamilino	n-propyl	137-138
	M1705	p-fluorosmilino	isopropyl	148-149
	M1804	p-chlorosnilino	ո-թՀորչ1	137–138
	х1813	L-chluroanfling	pheayl	113-115
	ML827	p-chlorophiling	p-1cobutyl-P(-methy)	lbensyl 179-182
	M1632	p-chlorusniline	3-pyridyl	223-224
	H2104	<u>n-mercaptoaniline</u> .	п-ргору1	164-166
	3210 6	o-mercsptusniino.	n·butyl	156
	X2107	u-mercaptoanilino	n-peaty L	135
	M21.13	o-mercapicoanilino	phonyl	168-169
30	K2116	o-mercaptosmilino	∑≐toÌÿl	160
	M2131	o-mercaptoamilimo	4-pyridyl	139-141
	M2205	m-trifluoromethylenilia	o : { вортору 1	108-109
		-	(כסמו	inved)

Pruduct	^k ² >n −	R ₃ -	Melting point (°C)
X2231	<u>m</u> -trifluoromethylanilino	4-pyrtdyl	229-230
162232	m-trifluoromethylamilino	3-pyridy1	220-221
132502	2,5-diethoxyanilio	methyl	1.78-1.80
N2504	2,5-dicthoxyaniline	n-propyl	147-148
112803	cyclohexylamino	athyl	147-149
м2816	eyelohenylamina	P-toly1	152-153.5
M5103	N-othylanilino	ethy1	136
K5132	W-sthylemilino	3-pyridyl	185-186

The s-trivaine derivatives (I) obtained by the processes of aspects of this invention act on the hormone system, especially the system of the diemosphalone, the pituitary gland and the adrenal gland, and remerkably increase the secretion of the internally induced conticold, waitly glacoconticold.

The experimental results concerning the toxicity, the increased secretion of glucocorticoid, and the pharmacoutical effect similar to that of adversal cortex hormons are shown below when a-triaxing derivatives (I) were administered.

Table 2 shows the result of the numerical calculation of the LD_{50} obtained by means of male mice. From the Table, it is seen that such s-triazines have very low toxicity, and are applicable to a very wide range of medical treatments.

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Table 2

Product	1.0 ₅₀ (mg/kg)	llye	Product	LD ₅₀ (ug/kg)	Ben
M1431	2700	p.o.	'X2't04	300	1.v.
M1.602	750	p. c.	M2205	> 5000	p.o
MJ 613	> 3000	p.0.	M2231	. > 3000	p.o.
м1702	1000	p.o.	M2232	> 3000	p.o.
ช1703	1000	p.D.	M3502	> 5000	p.o.
X1704	2000	p.o.		<i>≥</i> 300	L.v.
X1705	2000	p.o.	и2504	>> 5000	••••
M1804	1200	p.o.		>> 500	1.v.
บ1832	> 5000	5.0.			

(Remarks) p.o. stands for oral administration i.v. stands for intravenous administration

Nost of the s-triazine derivatives (I) of aspects of this invention promote the secretion of intercully induced corticoid.

Measurements were regularly made of the concentration of corticosterone, in the blood subsequent to the oral administration thereof to rats.

The results of the wescurements are shown in Table 3.

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Table 3

			Conticost	cone (pg/ml	plood blashed)	
Product	Dosa (mg/kg)	1 ihour	3 haurs		Value shown 7 hours -after admin- 1stration	Tota
X1403	600	68	65	102	107	343
M1431	200	70	110	6D	75	318
M1602	100	66	54	51	70	241
M1613	600	65	110	75	65	. 315
M1702	200	64	65 -	.54	40	2.23
M1703	200	49	65	.50	. 66	230
М1704	400	61	61	· 64	61	247
X1705	400	80	69	67	30	246
M1832 .	60D	76	55	70	45	240
×2104	20	300	30	45	30	40.5
N2106	500	75	98	71	. 73	307
112113	100	-	.45	5.5	37	137
n2116	44	44	47	28	53	172
и2131	34	65	52	70	81	. 291
M2205	200	75	67-	43	47	234
н2231	600	28	32	29	29	11
K2502	600	67	.57	43	71	23
Control	0	46	4	22	16	8

ACTH (administration tropic normal) and conticuid have the effect of increasing hepatic glycogen. Table 4 shows the degree of settlement of hepatic glycogen that is measured when the c-triszine derivatives (I) of aspects of this invention are administered to rate in a dame of 25 mg/ky and 5 mg/ky respectively.

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Table 4

The same of the sa	Quentity of Napatle Glycogen	(mg/g liver	
Product Dogs	25 mg/kg	5 mg/kg	
M1403	D.7&7 <u>+</u> 0.257	0.537 <u>+</u> 0.652	
кл.613	2.017 <u>+</u> 0.455	0.526+0.055	
MJ.703	1.70510.401	1.468 <u>+</u> 0.95B	
ML704	1.011-0.458	1.234+0.569	
к1705	1,583+0.541	0.52440,621	
ษ1804	3.43611.1/10	0.530 <u>+</u> 0.014	
M1832	1.931+0.548	0.700+0.385	
м2104		5.007 <u>+</u> 1.226	
M2116		1.608+0.834	
M2205	1.771+0.478	0.559 <u>+</u> 0.052	
K2231	1.072+0.163	1.363.40,422	
Ж2232	1.682 <u>+</u> 0.555	1.049+0.517	
Hydrocortisons	•	1.728+0.341	
Control	0.527 <u>+</u> 0.306	D.432 <u>+</u> D.129.	

Table 5 shows the effect on the thymns gland, the odrenal gland and the spleen which effects are measured after oral administration to rate.

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<u> Table 5</u>

•			Organ Gai	rgen Gain (%)		
Produc‡	Dose (mg/kg)	Thymns	Adrenal Gland	Syleen		
K1431	50	-2,6	79.5	-14,6		
	100	-10.5	40.2	-13.8		
M1632	50	-16.0	50.4	-12.4		
	1.00	-35,9	100.0	-20.5		
M1.702	50	-23.B	37.3	10.4		
	100	-22.0	38-6	6.1		
%1704	50	-15.B	43.1	10-1.		
•	100	-19.4	35.3	4.9		
м1705	50	-3.9	28.1	41.0		
	100	-11.9	34.6	18.0		
X1,832	59	-5.9	32.5	-32.5		
-	100	-7.2	53.8	-21.6		
H2106	31	-3.9	64.1	-1,4		
M2116	11	-8.8	35.0	-23.0		
-	22	2.0	47.9	8. lt.		
142131	. 8	15.0	28.2	-5.5.4		
	16	4.6	87.2	-7.3		
Hydrocorticone	50	-74.8	-39.7	24.1		

Conticoid has a very strong anti-inflammation effect. The administration of the s-triazine derivatives (I) of espects of this invention leads to an increase in the secretion of internally induced corticoid, and an anti-inflammation effect can be expected. Table 6 shows the results of oral administration thereof to rate.

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Table 6

_				Suppression ()	
1	Product	Dose (mg/kg)	Cotton-polle Assay	Carrageanin Induced Edema	
• ••	. •		Wet Weight	Dry Weight.	Tost
-	ж1403	100	~2	-28 ·	20
	·	50	30	31	68
	x1431 .	100	3	14	70
		50	25	29	28
i	×1802	75	11	46	57
		38	-1	33	25
	, M1702	100	-2	27	23
		50	7.3	13	46
	ж1704	100	. 28	37	74
		50	28	37	39
	M1.705	100	5	36	63
	<i>:</i>	50	18	8	55
	x2104	20	18	27	66
	-	. 10	1,8	40	29
Ō	ж2113	50	20	34	27
		25	39	54	43
	M2116	22	37	44	11
		11	28	32	. 33
	K27.31	17	33	23	Ĺ
		.9	21	17	1
	Corticosterone	50			32
		10*	21	23	
	Hydrocortison¢	50	41	41	53
		10*	44	48	

*Intravenous administration

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The oral or intravenous administration of the s-trinzine derivatives (I) of aspects of this invention to rais, cabbits and dogs will
result in a remarkable increase in the quantity of 17-0005 in the blood
and urine as compared to the group of controls. If the s-trinzine derivatives of espects of this invention are used together with a glucococticoid, the hormone effect thereof is remarkably increased.

From the showe-described pharmacological experiments, the following two effects can be noted concerning the s-triazine derivatives

(I) of aspects of this invention:

(1) Through the effect on the pituitary system and on the adrenal system, it causes an increase in the biosynthesis of the hormons, especially glucocorticoid.

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(2) Through the perticipation in the function of the hormone, it intensifies the performance of the hormone.

ACTH and corticoid have a large variety of physical and pharmacological effects, and thus they are used for various medical purposes; however, they are not free from many secondary ill effects. The most serious disadvantage of the continuous administration of corticoid is believed to be a decline to the performance of the adrenal cortex and a withdrawal syndrome.

ACTH shows the same offert as in the case of the administration of steroid, and one of its advantages is that the advantal cortex performance is not decreased and well-balanced secretion of coefficient from the advantages in that it must be used exclusively by injection, it is extremely exponence, and it is not free from cases of death from shock. Thus its clinical application is radically restricted.

The merit of the novel s-triazine compounds of aspects of this invention lies in the removal of the disadvantages of ACTH or corticold while providing the desirable effects of such compounds.

Because of the effect of the s-triazine compounds of aspects of this invention in increasing the secretion of internally induced

corticoid, one can expect from such compounds the same effect as from the administration of ACTN or norticoid in the same of the following diseases:

Kaphrotic syndroms

Bronchial asthma

Chronic arthrorheumstism

Wheumatic fever

Chronic hepstitis

Allargic disease

Malignant lymphoms

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Spinitis

and many other diseases that ere believed to be adopted to the administration of steroid agent.

The navel s-trissine compounds (f) of aspects of the present invention can be upplied in the form of any suitable medicinal composite in combination with other medicines as the case may be. They can be taken orally or otherwise. They can be administered in any pharmacount—cally possible form, for example, powders, respectes, pellets, granules, injections or suppositories.

from the data given above; it is noted that the s-triaxing derivatives of aspects of the present invention provide a new important substitute medicine in the field of the adrenal cortex staroid therepeutics.

Aspects of the present invention are illustrated by the following examples:

Example 1

2-Amino-4-(N-ethylamilinu)-6-(3-pyridyl)-1,3,5-triaxine

18.8 grams of N-othyl-E-phenyldicyandiamide and 10.5 grams of 3-cyanopyridine were added to a solution of 4 grams of potassium hydroxide in 60 al of ethyl celloculve and the mixture was refluxed under stirring for 3 hours. The solution was then poured into about 500 ml of bot water and the white crystals precipitated were collected by

coltration and convertablized from accionitrile. 19.5 grams of 2-amino-4-(N-othylamilino)-6-(3-pyridyl)-1,3,5-triazine having a melting point of 185 - 186°C, were thus obtained.

Elementary analysis for C16 16 16 16 16

Theoretical: C 65.74%, R 5.52%, N 28.75%

Experimental: C 65.53X, H 5.60%, N 29.00%

Example 2

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2-Amino-4-(N-sthylaniline)-6-ethyl-1,3,5-triazine

16.9 grams of N-ethyl-N-phenyldicyaudismide and 6.6 grams of princentrile were added to a solution of 3.2 grams of potassium hydroxide in 40 ml of mathyl cellosolve and the mixture was refluxed under starring for 2.5 hours. The solution was then poured into 300 ml of hot water and the white crystals precipitated were collected by filtration and recrystallized from acetonitrile. 13.8 grams of 2-amino-4-(N-exhylandlino)-6-othyl-1,3.5-trisxins having a melting point of 136°C. were thus obtained.

Flomentary enalysis for C131117115:

Theoretical: C 64.18%, H 7.04%, N 28.78%

Bapecimental: C 64.49%, R 7.22%, # 28.76%

This 2-amino-4-(R-ethylanilino)-6-ethyl-1,3,5-triszine were recrystallized from hydrochloric acid and the monohydrochloride was thus

obtained.

Elementary analysis for C13818 501:

Theoretical: 0 55.81%, H 6.49%, W 25.63%, El 12.67%

Experimental: C 56,07%, H 6,48%, M 24,99%, Cl 12.82%

Frample 3

2-Amino-4-(p-dilarosmilino)-6-phenyl-1,3,5-tylazine

3.0 grams of N-(p-thloropheny1)-dicyandiamide and 1.6 grams of betweenticile were added to a solution of 1.0 gram of addition mathylate in 10 mi of othyl cellosolve and the mixture was refluxed under stirring for 2 hours. 3 ml of water was then added to this solution and the mixture was then poured into 70 ml of water and the white crystals precipi-

tated were collected by filtration and recrystallized from n-butanol.

2.4 grams of 2-smino-4-(p-chlorosmillino)-6-phenyl-1,3,5-triagine having a mailting point of 114 - 115°C, were thus obtained.

Stementary analysis for C₁₅H₁₂K₅Cl:

Theoretical: C 60.51%, R 4.06%, N 23.52%, Cl 11.91% Experimental: C 60.76%, R 4.13%, N 23.80%, Cl 11.85%

When I equivalent of metanusulfonic acid was dropped into a dioxene solution of this 2-amino-4-(p-chloroscilino)-6-phenyl-1,3,5-triazino nucler cooling and attribug, the methemesulfonate was obtained.

10 Elementary analysis for C₁₆H₁₆N₅O₃CLS:

Theoretical: C 48.79%, H 4.09%, N 17.78%

Experimental: C 48.51%, n 4.26%, N 17.38%

Paample 4

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2-Amino-4-(p-chlorosmilino)-6-methyl-1,3,5-triaxine

2.0 grams of K-(p-chlorophenyl)-dicyandianide, 20 ml of acetonitrile and 1.5 grams of potentium hydroxide were heated under stirring. In this case the potentium hydroxide generally dissolves in the mixture. After reflexing for 5 hours, the solution was poured into het water and the white crystals precipitated were collected by filtration and recrystallised from a-butanol. 1.3 grams of 2-amino-4-(p-chloromilino)-6-methyl-1,3.5-triaxine having a welting point of 196 - 197°C. were thus obtained.

Elementary analysis for C10810K5CL:

Theoretical: C 50.96%, H 4.26%, N 29.72%, C1 15.04%

Experimental: C 50.71%, H 4.09%, N 30.10%, C1 14.85%.

When ethanol containing I equivalent of hydrochloric acid was added to an ethanol colution of this 2-anino-4-(p-chlorosnilino)-6-methyl-1,3,5-trisging, the monohydrochlorids was obtained. When I equivalent of acetylaelcyclic acid was used in the same way, the monoacetylaelicyclic addition salt was obtained.

Example 5

2-Audino-4- (n-butylimitus)-6-(3-pyridyl)-1,3,5-triaging

25.2 grams of N-m-butyldteyandiemide and 18.8 grams of 3-cyanopyriding were added to a solution of 10 grams of potimplima hydroxide in 100 mi of othyl cellusolve and the wixture was refluxed under stirring for 3 hours. The solution was then poured into 500 ml of hot water and the white crystals promipitated were collected by filtration and recrystallized from accommittile. 28.6 grams of 2-omino-4-(n-butylemino)-6-(3-pyridyl)=1,3,5-triazine having a multing point of 144.5 - 145.5°C. were thus obtained.

Elementary analysis for Classical No.

Theoretical.:

c 59.00Z, N 6.60c, N 34.40%

Experimental: C 58.842, H 6.62%, N 34.75%

Example 5

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2-dual-decyclohomy (smino-6-(p-tolyl)-1,3,5-triszine

33.0 grams of M-cyclohexyldicyaudiamide and 73.4 grams of p-mathylbenzonitrik; when added to a solution of 10 grams of potessium hydroxide in 100 ml of methyl callopolve and the mixture was refluxed under Stirring For 2 hours. The colution was then poured into 500 ml of hot water and the white crystals precipitated were collected by filtration and recrystallized from n-butanol. 60.0 grams of 2-amino-4-cyclohexylamino-6-(p-tolyl)-1,3,5-triazine having a melting point of 152 - 153.5°C. pore thus obtained.

Rlementary analysis for C16H21H5:

Theoretical:

C 67.82%, H 7.47%, N 24.71%

Experimental: C 68.00%, H 7.44%, B 24.85%

Example 7

2-Aminu-4-(2-brunosmilino)-6-vinyl-1,3,5-triazine

4,3 grams of N-(p-bromophymy1) dicyandiawide and 1.0 gram of acrylanitrile were added to a solution of 0.8 gram of potassice hydroxide in 20 mi of ethyl collosolve and the mixture was refluxed under stirring for 3 hours. After cooling, water was added to this solution and the mixture was then extracted with chloroform. After distilling off the chloroform, the residue was recrystallized from acetonitrile.

2.7 grams of 2-amino-4-(p-bromosnilino)-6-vinyl-1,3,5-trlazine having a multing point of 122 - 124°C. were thus obtained.

Riementary analysis for C₁₁N₁₀N₅Er:

Theoretical: C 45,232, H 3.452, N 23.97%

Experimental: C 45.20%, H 3.69%, K 23.82%

Example 8

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2-Amino-4-(p-fluoromnilino)-6-(n-propyl)-1,3,5-triazine

of n-butyronitrile were added to a unlution of 5 grams of potassium hydroxide in 100 ml of ethyl cellosolve and the mixture was refluxed under stirring for 3 hours. The solution was then powed into 500 ml of hot water and the white crystals precipitated were collected by filtration and recrystallized from a mixed solution of ethanol and water. 27.6 grams of 2-unino-4-(p-fluorosmilino)-6-(n-propyl)-1,3,5-triazine having a melting point of 137 - 138°C. were thus obtained. Elementary analysis for $C_{12}K_1k_2^M_5P$:

Theoretical: C 58,29%, H 5.71%, N 28.32%, F 7.68%

Experimental: C 57.94%, H 5.99%, N 28.17%, F 7.41%

Example 9

2-Amino-4-(m-trifituarowethylanilino)-6-(p-isobutylbenzyl)-1,3,5-triasine

25.0 gcms of m-aninobensotrifinoride and 13 grams of dicyandiamide were dissolved in 62 ml of 10% hydrochloric acid. The solution was refluxed for 1 hour. After cooling, the precipitated m-artifluoromethylphemyldiguanide hydrochloride was collected by filtration, washed with water and dried.

14.1 grams of this m-trifluorouethylphenyldiguanide hydrochloride were added to a solution of 1.2 grams of wetallic sodium in 70 ml of methanol and the mixture was stirred. 11.0 grams of othyl primbutylphenylametate were then added to the solution, which was left at room temperature for 72 hours. At the end of this time, water was added in an amount of twice the volume of the reactant solution, which was allowed to cool. Crystals precipitated thereby were collected by

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filtration and recrystallized from a wixed solvent of athomal and vater.

11.6 grams of 2-amino-4-(m-triffine comethy/smilino)-6-(p-1sobutylbrozyl)
1,3,5-tringine were thus obtained.

Riementary analysis for C21H22R5F3:

Theoretical:

C 62,83%, H 5.52%, N 17.45%

Experimental:

c 62.71%, H 5.50%, N 17.39%

Example 10

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2-Amino-4-cyclohexylomino-6-ethyl-1,1,5-triaxine

34.5 grams of cyclobexylamino hydrochloride and 21.5 grams of dicyandismide were uniformly ground together. The mixture was welted as oil bath at 150 - 160°C, and maintained at this temperature for about 30 minutes. It was then cooled, dissolved in but methanol and the solution moded. Cycloboxylamanide hydrochloride was thereby precipitated.

added to a solution of 1.2 grass of metallic sodium in 40 ml of methanul, 5.2 grass of chtyl propionate were then added and the mixture was stirred. After leaving the mixture at room temeprature for 72 hours, water was added thereto in an amount twice the volume of the reacting solution, to precipitate white crystals. The precipitated crystals were collected by filtration and recrystallized from a mixed solvent of ethanol and mater. 8.4 grass of 2-amino-4-cyclobecylemino-6-acthyl-1,3,5-triazine having a melting point of 147 - 149°C, were thus obtained. Elementary analysis for $C_{11}\Pi_{18}K_5$:

Theoretical.:

e 59.97%, n 8.24%, N 31.79%

Experimental:

C 60.28%, n 8.21%, N 31.81%

Example 11

2-Amino-4-(p-fluormanilino)-6-chyl-1,3,5-triaxine

80.5 grams of p-fluoraniline and 61.2 grams of dicyandianide were dissolved in 290 whof 10% hydrochloric acid and the solution was refluxed for 1 hour. After cooling, p-fluorophonyidizuanide hydrochloride, which was precipitated, was collected by filtration and dried.

11.5 grams of this p-fluorophenyldiguanide hydrochioride were added to a solution of 1.5 grams of metallic sodium in 70 al of aethural.

5.2 grams of ethyl propionate were then added and the mixture was stirred. After leaving the mixture at room temperature for 72 hours, water was added in an amount twice the volume of the solution and the mixture was allowed to cool. The crystals so precupitated were collected by filtration and recrystallized from n-betanel. S.1 grams of 2-amino-4-(2-fluoroemiline)-6-othyl-1.3.5-trisxine having a melting point of 160 - 161°C, were thereby obtained.

Blementary analysis for C14H12M5F:

Theoretical: C 56.64%, H 5.19%, R 30.03%

Experimental: C 36,49%, H 4.96%, N 30.00%

Example 12

2-kmino-4-(n-hαεγlawino)-6-(p-isobutylbenzyl)-1.,3,5-triszins

50 grams of n-butylamine bydrochloride and 38.4 grams of dicyandismide were uniformly mixed and then welted on an oil bath at a temperature of 130 ±5°C. The mixture was maintained at this temperature for about 4 hours and then cooled. After cooling the mixture was dissolved in hot methanol and again cooled, precipitating n-butyldiquenide hydrochlorids.

9.7 grams of them n-butyldiguanide hydrochloride were added to a solution of 1.5 grams of metallic sodium in 50 ml of methanol, 11.0 grams of ethyl p-isobutylphenylacetate were added therefor and the mixture was stirred. After leaving the mixture for 72 hours, water was added thereto in an amount twire the volume of the reacting solution. Crystals were precipitated, were collected by filtration and were recrystallized from a mixed solvent of ethenol and water. 13.5 grams of 2-amino-4-(n-butylamino)-6-(p-isobutylbensyl)-1.3.5-triasine having a melting point of 99.5 - 101°C, were thereby obtained.

30 Elementary analysis for C18112715:

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Theoretical: C 68.97%, H 6.68%, N 22.34%

Experimental: E 69.17%, R 8.79%, R 22.322

Example 13

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2-Amino-4-(p-bromosnilino)-6-ethyl-1.3,5-trlazine

If grams of p-bromosnilino hydrochloride and 8.4 grams of dinyandiamide were dissolved in 40 oil of water and the solution was refluxed for 1 hour. The solution was then cooled and the p-bromophenyl-diguanide hydrochloride thus precipitated was collected by filtration, washed with water and dried.

5.4 grams of this p-bromophenyldiquanide hydrochloride were dissolved under stirring in a solution of 10 grams of caustic anda in 10 ml of water and 10 ml of diceans and 5.1 ml of propionic subydride was dropped into the solution at a temperature between 50 and 55°C.

1 hour after the completion of dropping, the crystals precipitated by addition of 70 ml of water were filtered and recrystalized from n-bucsmol. 4.4 grams of 2-anino-4-(p-bromoanilino)-6-ethyl-1,3.5-triazine having a melting point of 178 - 180°C. were thus obtained.

Example 14

2-Emino-4-(p-mathylan(lina)-6-methyl-1,3,5-triazins

14.4 grams of p-toluiding hydrochloride and 8.4 grams of dicyandismide were dissolved in 40 mk of water and the solution was refluxed for 1 hour. The solution was then cooled and the p-methylphenyl-diguanide hydrochloride thus precipitated was collected by full ration, washed with water and dried.

4.2 grams of this p-mathylphonyldigumide hydrochloride was dissolved under stirring in a solution of 10 grams of caustic sods in 10 ml of water and 10 ml of dioxage and 4 ml of scatic subydride was dropped into the solution at a temperature between 50 and 60°C. I hour efter the completion of the dropping, the crystals productated by addition of 70 ml of water were filtered and recrystallized from n-butago).

3.2 grams of 2-amino-4-(p-methylamilino)-6-wethyl-1,3,5-atthexime having a melting point of 170 - 172°C, were thus obtained.

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